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Medical and surgical aspects of parathyroidectomy

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Medical and surgical aspects of parathyroidectomy. A more logical approach to the management of the chronic dialysis patient with parathyroid hyperplasia has become possible thanks to recent progress in cellular and molecular analysis of surgically removed parathyroid glands and accumulation of clinical experience. When one or more parathyroid glands progress to the stage of nodular hyperplasia, it is usually difficult to control PTH secretion even by calcitriol pulse therapy. For such patients, we have developed two new therapeutic approaches, i.e., selective percutaneous ethanol injection therapy (PEIT) and direct calcitriol injection therapy, in combination with medical therapy. For optimal selection of therapeutic modalities it is indispensable to evaluate the degree and stage of parathyroid hyperplasia. For successful management, prevention of nodular hyperplasia is the most important strategy.

Hyperplasia of parathyroid glands is one of the characteristic features of very severe secondary hyperparathyroidism in chronic dialysis patients [1]. We have been accumulating basic and clinical data on parathyroid hyperplasia in the last l0 years. Such information has provided us with more options of treatment, either medical or surgical, and more logical approaches to these patients.

WHAT HAVE WE LEARNED FROM SURGICAL PARATHYROIDECTOMY?

Large parathyroid glands in dialysis patients usually show asymmetrical enlargement and nodule formation. There are two types of parathyroid hyperplasia, diffuse hyperplasia and nodular hyperplasia; usually nodules are surrounded by a fibrous capsule. Nodular hyperplasia is the more advanced type of hyperplasia and is seen more often in large glands. The characteristics of cells in nodular and diffuse hyperplasia are strikingly different [2].

In nodular hyperplasia the sigmoidal curve, relating PTH secretion to the concentration of ionized calcium, is shifted to the right, i.e., a higher concentration of ionized calcium is needed to suppress PTH secretion [3]. Furthermore, parathyroid glands with nodular hyperplasia cells express more Ki67 (a kind of proliferative nuclear antigen), retinoblastoma protein, and cyclin D1 than do cells in diffuse hyperplasia [4]. Apparently in nodular hyperplasia the growth potential of parathyroid cells is higher than in diffuse hyperplasia. As recently shown by using X chromosome inactivation with PCR and restriction enzyme digestion, monoclonal proliferation may be present irrespective of the size of the nodule [5]. By contrast, cells in parathyroid glands with diffuse hyperplasia are always of polyclonal origin.

Additional information was derived from the analysis of transplanted fragments of parathyroid glands. As shown in Fig. 1 (right), in patients undergoing total parathyroidectomy with autotransplantation, surgeons select fragments for transplantation from the smallest gland [6]. Nevertheless, recurrence of hyperparathyroidism is sometimes encountered. A large-scale follow-up study revealed that the recurrence rate was significantly less frequent than from diffuse hyperplasia. The cells in the fragments of patients who had recurrence of hyperparathyroidism exhibited high growth potential comparable to that of cells in nodular hyperplasia, as assessed by flow cytometry [7].

CELLULAR PATHOGENESIS OF PARATHYROID HYPERPLASIA

What are the mechanisms underlying such abnormalities of parathyroid cells in nodular hyperplasia? We examined the density of vitamin D receptors in these cells and found that cells in nodular hyperplasia had a significantly lower density of vitamin D receptors than those in diffuse hyperplasia [8]. A significant negative relationship was found between Vitamin D receptor density and the number of PCNA positive cells or gland weight [9]. Recently, a decrease of calcium sensing receptors in nodular hyperplasia has also been demonstrated [10].

Parathyroid hyperplasia progresses from diffuse to nod-

Key words: chronic dialysis, parathyroid hyperplasia, parathyroid hormone, percutaneous ethanol injection therapy.

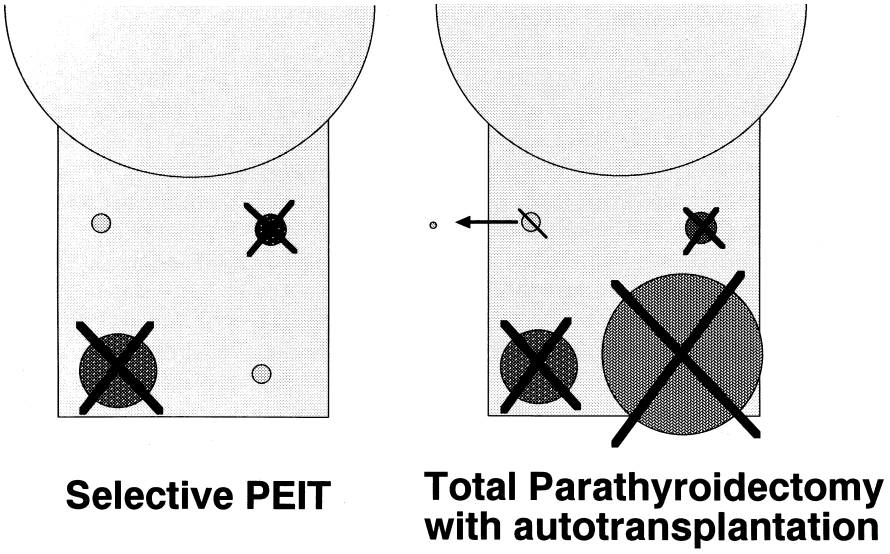

Fig. 1. Selective PEIT and surgical parathyroidectomy. In selective PEIT (left), glands with nodular hyperplasia are destroyed by ethanol injection (X) and the other glands with diffuse hyperplasia are controlled by medical therapy. In the surgical parathyroidectomy (right), all glands are excised (X) and fragments from the smallest gland (\) are transplanted.

ular hyperplasia. Some cells with more pronounced reduction of vitamin D receptor and calcium-sensing receptor in areas of diffuse hyperplasia begin to proliferate more vigorously leading to formation of individual nodules and finally to nodular hyperplasia. In very severe cases, one of the nodules outgrow the others so as to occupy the whole gland, forming a single nodule. This is the most advanced type of parathyroid hyperplasia in uremia.

CLINICAL IMPLICATIONS OF PARATHRYOID HYPERPLASIA

As can be deduced from the pathogenesis, parathyroid cells in parathyroid glands with nodular hyperplasia are usually resistant to medical therapy. Accordingly, for optimal selection of therapeutic modalities, it is critical to distinguish between diffuse and nodular hyperplasia.

Our experience with calcitriol pulse therapy shows that one useful index may be the size of the gland. In patients who have small parathyroid gland(s), PTH secretion was easily suppressed by calcitriol pulse therapy, and subsequently the patients were well controlled by conventional oral vitamin D therapy. By contrast, PTH was not controlled in the long term in patients who had relatively large parathyroid gland(s). This observation suggests that larger glands are more resistant to calcitriol than smaller glands. In our experience, patients with at least one gland larger than 0.5 cm^3, or 1 cm in diameter, are usually refractory to calcitriol pulse therapy in the long term [11]. Independently, it has also been shown that transplanted parathyroid fragments derived from glands weighing more than 0.5 g relapse frequently [12].

Since gland size and weight correlate very well, this size seems to be critical to predict resistance to medical therapy. A histologic study of surgically removed parathyroid glands revealed that most of the parathyroid glands weighing more than 0.5 g exhibited nodular hyperplasia [12].

One can predict the existence of nodular hyperplasia by estimating gland size, which can be done most easily by ultrasonography. The shape of the enlarged glands can also be assessed by the latest generation of ultrasonographic devices and this also provides helpful information. In addition, blood supply to the glands can also serve as a marker for nodular hyperplasia. Blood supply to enlarged parathyroid glands can be detected by color Doppler ultrasonography, especially using the power mode [13]. A recent preliminary report suggests that most of the enlarged glands with detectable blood supply within the gland exhibited nodular hyperplasia. Quantitative evaluation of blood supply is mandatory for precise recognition of nodular hyperplasia.

MANAGEMENT OF PATIENTS WITH NODULAR HYPERPLASIA

How can one manage patients with nodular hyperplasia? Needless to say, prevention of nodular hyperplasia is the best strategy. For this purpose, control of serum phosphate seems very important. A high concentration of phosphate directly stimulates synthesis and secretion of PTH. Such stimulation was more evident in glands with diffuse than with nodular hyperplasia [14]. These data suggest that the sensing mechanism for phosphate is maintained only in cells in areas of diffuse hyperplasia. Thus, phosphate control is important for the prevention of parathyroid hyperplasia especially in the early phase of secondary hyperparathyroidism.

Until recently, patients with nodular hyperplasia have been treated by calcitriol pulse therapy which failed to

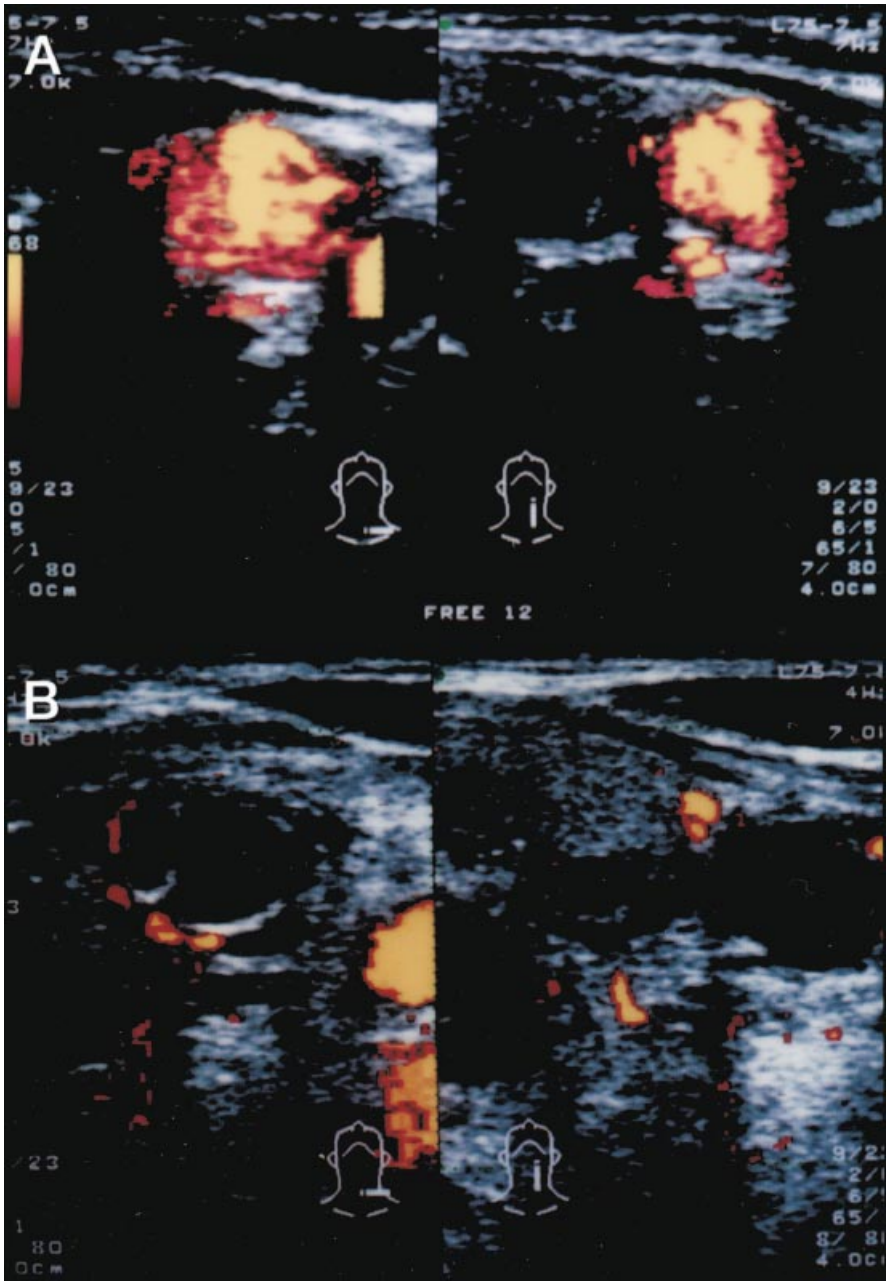

Fig. 2. Color Doppler imaging of parathyroid hyperplasia (transverse, left; sagittal, right). (*A*) Ample blood supply was demonstrated in the markedly enlarged parathyroid gland with power Doppler mode. (*B*) Blood supply inside of the gland disappeared after the first ethanol injection. Some nodules surrounded by the blood supply to the surface of the gland were recognized.

effectively suppress PTH and result in hypercalcemia in most cases. Only in advanced cases was surgical parathyroidectomy considered. For such patients, a new strategy has recently been established i.e., selective percutaneous ethanol injection therapy (PEIT) of the parathyroid gland [15]. This technique is no longer only an alternative to surgical parathyroidectomy, but serves also as a powerful adjunct to medical therapy. As shown in Figure 1, in surgical parathyroidectomy all glands are excised and fragments taken from the smallest gland are transplanted. By contrast, in selective PEIT, all glands with nodular hyperplasia are selectively destroyed by ethanol and the remaining glands with diffuse hyperplasia are controlled by medical therapy (Fig. 1). Thanks to technological progresses, we can now perform PEIT more efficiently and safely than ever.

The indication for PEIT is almost the same as that for surgical parathyroidectomy, i.e., high turnover bone disease due to high PTH, marked parathyroid hyperplasia, and resistance to medical therapy. In such patients all glands larger than 0.5 cm^3 should be destroyed to achieve effective control of parathyroid function. Patients with one or two enlarged glands with nodular hyperplasia are good candidates for this therapy.

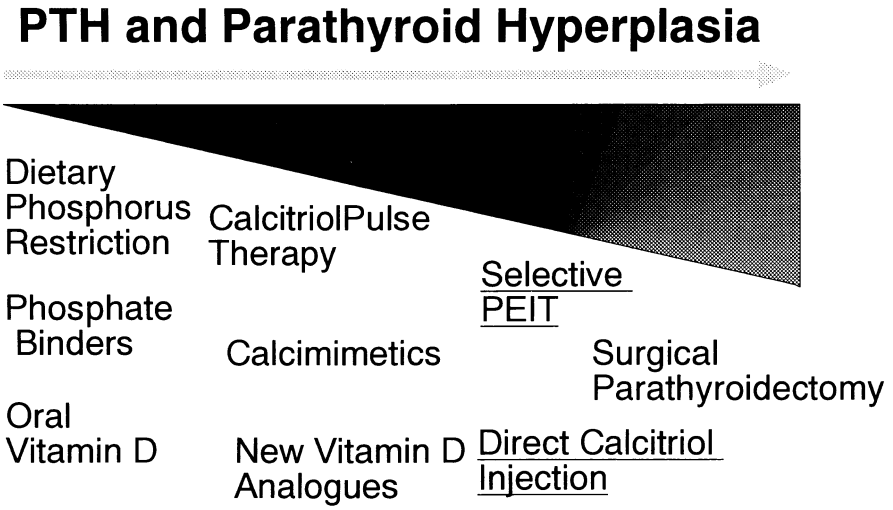

Fig. 3. Currently available therapeutic modalities for hyperparathyroidism in dialysis patients. There are many options for treatment depending on PTH levels and the degrees of parathyroid hyperplasia. For patients with one or two enlarged glands with nodular hyperplasia, "selective PEIT" or "direct calcitriol injection" can be the choice of treatment in combination with medical therapy.

According to the survey by Japanese working group on PEIT of parathyroid, more than 600 patients have been treated by PEIT at nearly l00 facilities in Japan. A decrease of PTH was confirmed in all patients and management by medical therapy became possible in more than 75% of patients.

We routinely use Doppler color imaging to confirm the destruction of the tissue, to recognize the recurrence of cell growth, and to optimize the site and the volume of additional ethanol injection (Fig. 2). Having developed several measures to minimize leak of ethanol from the gland, we have now achieved a very low rate of complications. As reported before, PEIT was successful when several protocols with different intervals between ethanol injections were used [15–17]. In contrast to surgical parathyroidectomy, the risk of hypoparathyroidism was minimal [17]. One can inject not only ethanol, but also other agents, such as calcitriol solution as we have reported [18]. This novel approach can be categorized as "pharmacological parathyroidectomy".

CONCLUSION

Figure 3 shows the currently available therapeutic modalities for secondary hyperparathyroidism in chronic renal failure. New vitamin D analogs and calcimimetics may be effective for those patients who can not be controlled by calcitriol pulse therapy. In addition, we have new strategies other than surgical parathyroidectomy.

As we discussed in this review, evaluation of parathyroidectomy hyperplasia is important not only for surgical parathyroidectomy, but also for the selection of medical therapy. We now have sufficient reason to abandon useless calcitriol pulse therapy in patients with enlarged parathyroid glands.

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